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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,591	08/27/2003	Noubar B. Afeyan	COTH-P02-001	7918

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EXAMINER	
MEAH, MOHAMMAD Y	
ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,591	AFEYAN ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,19-34 and 37-40* is/are pending in the application.

4a) Of the above claim(s) *3,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,19-27,30-34 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-5, 19-34 and 37-40 are pending. With supplemental amendment, filed 4/17/09, in response the final action, mailed on 1/26/2009, the applicants amended claims 1, 21, 23-25, 28, 30-31 and 33-34 and canceled claims 41 and 14-17. Claims 3 and 28-29 remain withdrawn.

Applicants' amendment of 4/17/09 is considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejection 35 U.S.C 112 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-5, 19-27, 30-34 and 37-40 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 4-5, 19-27, 30-34, 37-40 (depend on claim 1) remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of the phrase in claim 1 "address site" because it is unclear what is the "address site". If it is merely a site which can be targeted by something, the term "address" makes it confusing. It should simply say "site" unless the term "address" is further defining where/what the site is. Correction is required.

Applicants' argument is considered but not found persuasive, because the term "address" is not clearly defined in the specification.

Claim 1 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of the phrase "resistant to cleavage by said protease domain" because the resulting claim does not set forth the metes and bound of the desired patent protection. The term "resistant" is a term of degree. It is unclear how much cleavage is required for the adzyme to be considered "resistant". The specification fails to disclose a definition of what is considered "resistant". Therefore, one of skill in the art is not able to determine the boundary of the claim. For the examination purpose only, the phrase is ignored because no reasonable interpretation could be made.

Applicants' argument is considered but not found persuasive, because the term "resistant" is a term of degree. It is unclear how much cleavage is required for the adzyme to be considered "resistant".

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of " the adzyme is resistant to autocatalyzed proteolysis at a concentration equal to –" because it does not further limit the subject matter of the claim from that of the previous claim 1. There is no actual value in the claim for the concentration of the adzyme in a solution to be administered to a subject. Therefore, it is unclear what it mean by "the adzyme is resistant to autocatalyzed proteolysis at a concentration equal to" something that is undefined.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of the phrase "resistant to autocatalyzed--" , because the resulting claim does not set forth the metes and bound of the desired patent protection. The term "resistant" is a term of degree. It is unclear how much cleavage is required for the

adzyme to be considered "resistant". The specification fails to disclose a definition of what is considered “resistant”. Therefore, one of skill in the art is not able to determine the boundary of the claim. For examination purpose a protein resistant to cleavage could be any protein stable enough to shows activity.

Applicants' argument is considered but not found persuasive, because the term “resistant” is a term of degree. It is unclear how much cleavage is required for the adzyme to be considered "resistant".

Claim Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a)A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of claims 1, 4, 19-27, 30-34 and 37 under 35 U.S.C. 103(a) by Davis et al (WO00/64485) in view of Chamow et al (Trend Biotech, 1996, 14, pp52-60) is maintained as discussed in the prior office action and restated again below:

Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, matrix metaloprotease, etc) which catalyze degradation of a specific target are conjugated to targeting (bind to the target) domains, such as ligand, antibody (page 23, lines 15-30, page 8 lines 20-25, page 15 lines 9-52), wherein protease is

conjugated to immunoglobulin, Fab or $F(ab)_2$). Davis et al teach that resulting chimeric protein has greater (catalytic, page 8) activity than the unconjugated molecule. The chimeric protein of Davis et al. binds to the target and antagonize/inhibit /degrade a wide variety of receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc (page 28). Davis et al. use the fusion protein as a pharmaceutical composition (pages 51-56). Although Davis et al do not teach the fusion proteins that are resistant to autoproteolytic cleavage, there is no available evidence to suggest that they are labile to autoproteolysis because their fusion proteins are stable enough to show protease activity to cleave substrate polypeptide they must inherently be resistant to self cleavage.

However Davis et al do not teach a fusion complex comprising fusion protein comprising protease conjugated to constant portion of immunoglobulin heavy chain and second fusion protein comprising a targeting domain conjugated to constant portion of an immunoglobulin heavy chain.

Chamow et al teach bispecific immunoadhesins (immunoglobulin fusion protein) comprising two different proteins having different functions each conjugated to each pair of constant region of immunoglobulin (table 1 and Fig 3, P-selectin-IgG and E-selectin-IgG). It is well known in the art the advantages of using the immunoglobulin constant region to make fusion proteins (see, Chamow et al, Trend Biotech, 1996, 14, pp52-60, and Ashkenazi et al, Current Opn. of Immonul. 1997, 9, pp 195-200): such as joining the fusion partner to immunoglobulin facilitates proper folding of domains and function (page 52 right column 2nd parg. Chamow et al) by providing antibody type

structural properties (by bring them closer, Ashkenazi et al, page 196 left column 2nd parg) and increase size often extend in vivo half-life (Ashkenazi et al, page 196 left column 2nd parg.). Therefore, one of skill in the art would have been **motivated** to make the fusion complex comprising a protease conjugated to constant portion of immunoglobulin heavy chain and a targeting domain conjugated to constant portion of an immunoglobulin heavy chain so that said catalytic domain and targeting domain fusion complex comprise proper folding (via immunoglobulin dimmeric binding partner) so that their effective concentration and function is optimized at the target site.

As such it would have been obvious to one of ordinary skill in the art to use a protease to make a fusion protein (adzyme) as taught by Davis et al and Chamow et al, wherein protease is conjugated to the constant region of an immunoglobulin heavy chain and a targeting domain comprising an antibody light chain is conjugated to the constant portion of another immunoglobulin heavy chain and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide. One of ordinary skill in the art at the time of the invention was made would have had a reasonable expectation for success for making an adzyme comprising a fusion complex comprising protease conjugated to constant portion of immunoglobulin heavy chain and a targeting domain conjugated to constant portion of an immunoglobulin heavy chain, because the DNA molecules encoding many proteases are known, and the molecular biology techniques required to make a recombinant fusion proteins are well known in the art (Ashkenazi et al, Current Opn. of Immonul. 1997, 9, pp 195-20). Claims 4, 21-22, and 30-34 are included in rejection because the

adzyme of Davis et al. and Chamow et al. meets all the structure limitations of the claimed invention and the additional limitations in claims 4, 21-22, and 30-34 appears to be intended uses of the claimed invention. Intended use limitations do not carry a patentable weight. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Rejection of claim 5 under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/64485) in view of Chamow et al (Trend Biotech, 1996, 14, pp52-60) as applied to claims 1, 4, 19-27, 30-34 and 37 above, and further in view of Dolinar et al. (*Food tecnol and biotech*. 2000, 38, 5-9) is maintained as discussed in the prior office action and restated again below:

Davis et al. and Chamow et al are described above. However neither Davis et al. nor Chamow et al. teach purification of a fusion protein comprising a protease domain using a reversible protease inhibitor.

Use of protease inhibitor in protein purification is well known in prior art. Dolinar et al. teach MMTS (methyl methane-thiosulfonate), a reversible protease inhibitor in the purification and refolding of a cystine proteinase type protein (page 6, column 2 last parg.). Therefore, one of skill in the art would have been **motivated to** purify **a** fusion protein complex comprising a protease using a protease inhibitor so that said fusion protein complex would not be cleaved by the protease.

As such it would have been obvious to one of ordinary skill in the art to use a protease inhibitor to purify the protease-containing fusion protein complex of Davis et al.

and Chamow et al. described above. One of ordinary skill in the art has a reasonable expectation of success at is obtaining an adzyme which is resistant to autocatalytic proteolysis in view of the teachings of Dolinar et al. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Rejection of Claims 38-40 under 35 U.S.C. 103(a) as being unpatentable over 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) in view of Chamow et al (Trend Biotech, 1996, 14, pp52-60) as applied to claims 1, 4, 19-27, 30-34 and 37 above, and further in view of Sanderson et al. (Medic. Res Rev 1999, 19, 179-197) is maintained as discussed in the prior office action and restated again below:

Davis et al. and Chamow et al. are described above. However, neither Davis et al. nor Chamow et al. teach a pharmaceutical preparation comprising a reversible inhibitor safe to humans.

Sanderson *et al.* (Medic. Res Rev 1999, 19, 179-197) teach a small molecule non-covalent binding protease inhibitor used in a pharmaceutical composition which is reversible and safe to humans (abstract).

Use of protease inhibitors in protein samples is well known in prior art because proteases catalyze the degradation of protein molecules (abstract, page 1, Sanderson et al).). Therefore, in order to inhibit the protease degradation of a pharmaceutical preparation comprising the adzyme of Davis et al. and Chamow et al., one of skill in the

art would have been **motivated** to add a reversible protease inhibitor that is safe to humans as taught by Sanderson *et al.* to extend the shelf life of the adzyme.

As such it would have been obvious to one of ordinary skill in the art to make a pharmaceutical preparation comprising the adzyme of Davis et al. and Chamow et al. and combine it with a reversible protease inhibitor as taught by Sanderson et al. so that said pharmaceutical preparation is safe to humans and remains effective. One of ordinary skill in the art has a reasonable expectation of success at making such pharmaceutical composition in view of the fact that protease inhibitors which are safe for humans are known and used in the art as evidenced by Sanderson et al. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Argument

Applicants' arguments files on 10/27/09 have been fully considered, but they found unpersuasive. Applicants argue that their invention is not disclosed nor suggested by the cited prior arts and that the skilled person would have little expectation of success in combining the cited references to derive their invention. Applicants' arguments have been fully considered, but they found unpersuasive. Applicants' argue that Davis et al. do not teach an adzyme (chimeric protein) that resistant to cleavage by protease domain and Chamow et al do not teach chimeric protein containing proteases. If any of these prior art teach applicants adzyme it would anticipate applicant invention. Furthermore, as explained in USC 35 112 2nd rejection, since "resistant" is a relative term, a protein resistant to cleavage could be any protein stable enough to shows

activity. Davis et al teach such a chimeric protein comprising protease (not only lectin as applicants suggested, page 23, lines 15-30, page 8 lines 20-25, page 15 lines 9-52) conjugated to an antibody. Although Davis et al. did not mention the resistivity to auto proteolysis, there is no available evidence to suggest that they are labile to autoproteolysis and furthermore, as their fusion proteins are stable enough to bind to the target and show protease activity to cleave substrate polypeptide, they must inherently be resistant to self cleavage. Applicants further argue that Davis et al teach chimeric protein wherein said chimeric protein is chemically cross-linked protein conjugate and Davis et al. especially teach advantage of chemical cross-linking and therefore one will not motivate to use cotranslation gene fusion technique. Applicants' arguments have been fully considered, but they found unpersuasive. As explained in the prior office action of 01/26/09. Bhatia et al (Intl. J. Cancer 2000, 85, 571-577, page 571, 3rd paragraph) provide motivation to make fusion protein by gene fusion method as it teaches the advantages of the recombinant fusion protein such as easier to make, one well defined product obtained, and higher purity product compare to chemical conjugation. Thus one of ordinary skill in the art would have been **motivated** at the time of invention to make protein conjugate comprising two protein partners of Davis et al by gene fusion methodology (as taught by Bhatia et al). Applicants argument about the rejection of claims 21-22 and 30-34 is considered but found unpersuasive because as explained in the office action and described above, these are use claims and it is obvious to use the prior art chimeric claims.

Applicants argument for the rejection of claim 5 regarding the use of Dolinar et al in combination of Davis et al. and Chamow et al. is fully considered, but it is found unpersuasive. Dolinar et al teach protease inhibitior in the purification process of proteins, therefore it would have been obvious to use protease inhibitior to purify fusion protein of Davis et al. or Chamow et al. as described above.

Applicants argument for the rejection of claims 38-40 regarding the use of Sanderson *et al.* in combination of Davis et al. and Chamow et al. is fully considered, but it is found unpersuasive. Sanderson *et al.* teach a small molecule non-covalent binding protease inhibitor used in a pharmaceutical composition which is reversible and safe to humans (abstract). Use of protease inhibitors in protein samples is well known in prior art because proteases catalyze the degradation of protein molecules (abstract, page 1, Sanderson et al).). Therefore, in order to inhibit the protease degradation of a pharmaceutical preparation comprising the adzyme of Davis et al. and Chamow et al., one of skill in the art would have been **motivated** to add a reversible protease inhibitor that is safe to humans as taught by Sanderson *et al.* to extend the shelf life of the adzyme.

Double Patenting Rejection

The provisional rejection of claims 1, 4-5, 19-27, 30-34, 37-40 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-5, 19-27, 30-34, 37-40 of copending Application No.10/792498 is maintained.

Examiner agrees with applicant that the provisional double patenting rejections may be withdrawn when all claims are otherwise allowable if the copending application is not allowable. All the examined claims of the instant application are rejectable on other grounds. Since applicant did not submit terminal disclaimer , the rejections will be maintained.

The provisional rejection of claims 1, 4-5, 19-27, 30-34, 37-40 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-38, 40-46, 52-60, 66-104, 107-134 of copending Application No.10/650,592 is withdrawn because, after amendment of claims 1, 4-5, 19-27, 30-34, 37-40 of the instant application, none of the claims of Application No: 10/650,592 render the claims of instant application obvious.

Allowable Subject Matter/Conclusion

None of the claims are allowable

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mohammad Younus Meah
Examiner, Art Unit 1652

/Ganapathirama Raghu/
Patent Examiner
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